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Merck
c/o Sirna Therapeutics, Inc.
1700 Owens Street
4th Floor
San Francisco, CA 94158

EXAMINER	
BOWMAN, AMY HUDSON	
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marilyn_moy@merck.com
catherine_naughton@merck.com

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/720,448
Filing Date: November 24, 2003
Appellant(s): MCSWIGGEN ET AL.

Peter Haeberli
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 8/11/10 appealing from the Office action mailed 7/12/10.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828).

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 52 and 54-64 are rejected and presently pending.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being

maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888)

Nyce (WO 99/13886)

Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000)

Matulic-Adamic et al. (US 5,998,203)

Bertrand et al. (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004)

Braasch et al. (Biochemistry, 2002, Vol. 41, No. 14, pages 4503-4510)

Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52 and 54-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Nyce (WO 99/13886), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), Matulic-Adamic et al. (US 5,998,203), Bertrand et al. (Biochemical and Biophysical Research Communications, 2002, 296, pages 1000-1004), Braasch et al. (Biochemistry, 2002, Vol. 41, No. 14, pages 4503-4510), and Olie et al. (Biochimica et Biophysica Acta, 2002, 1576, pages 101-109).

The instant claims are directed to a siRNA molecule having a sense and an antisense strand wherein both strands comprise 10 or more 2'-deoxy, 2'O-methyl, 2'-deoxy-2'-flouro, or universal base modified nucleotides and the sense strand comprises a terminal cap at one or both ends. The claims are further directed to 10 or more pyrimidines of the sense and/or antisense strand to be 2'-deoxy, 2'O-methyl, or 2'-deoxy-2'-flouro; the sense and/or antisense strand comprises phosphorothioates, and to a composition comprising the siRNA molecule and a pharmaceutically acceptable carrier.

Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. The siRNAs taught by Elbashir et al. mediated RNAi via RISC. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications that retained activity.

Elbashir et al. teaches that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function (see page 6886, column 2); modifying terminal nucleotides (see page 6881), meeting the instant limitation of a terminal cap; the siRNA molecules comprise ribonucleotides (see Fig. 1, for example); duplexes of 21 nt siRNAs with 2 nt 3'-overhangs were the most efficient triggers of sequence-specific mRNA degradation (see abstract, for example); modification of the overhangs (see page 6881); wherein the siRNA is in a composition with a pharmaceutically acceptable diluent, such as buffer (see Materials and methods, page 6886).

Elbashir et al. do not teach double stranded nucleic acid molecules with combinations of modifications at the instant number of positions and do not teach phosphorothioates.

Elbashir et al. do not teach 2'-deoxy-2'-flouro modifications, although the only claims that require such are claims 58 and 64, as this is just one species of the genus of the remainder of the claims.

Nyce teaches antisense oligonucleotides that attenuate the expression of target mRNA. The oligonucleotides are preferably up to about 30 nucleotides in length, more preferably up to about 21 nucleotides in length (see page 16). Nyce teaches antisense oligonucleotides targeted specifically to human muscarinic acetylcholine receptor 3 (CHRM3) (see page 54). Nyce teaches phosphorothioate, 2'-deoxy and 2'-O-methyl modification of the oligonucleotides at various percentages of the purine and/or pyrimidine residues, including 100% substitution (see page 73) for enhancing the uptake of the oligonucleotides. The 100% substituted oligonucleotide comprises a phosphorothioate at the 3' end. Nyce teaches compositions comprising the oligonucleotide and a pharmaceutically acceptable carrier (see page 77). Nyce teaches surfactants or surfactant components bound to the 5' and/or 3' ends or the oligonucleotides for enhancing uptake of the oligonucleotide (see page 80).

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-

Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, CL and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with complete modification with 2'-fluorouracil modifications. However, it is noted that the instant claims do not recite any upper length limitation. Furthermore, the extensively modified dsRNA of Parrish et al. resulted in strong RNAi activity.

Bertrand et al. teach a comparison of antisense oligonucleotides and siRNAs. Bertrand et al. teach that siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides. Bertrand et al. teach that siRNA activity, but no antisense oligonucleotide activity, was observed in mice, probably due to

the lower resistance to nuclease degradation of antisense oligonucleotides (see abstract). Bertrand et al. teach that siRNAs are composed of small double-stranded RNA oligonucleotides with a length of 21/22 bases (see page 1000, column 1). Bertrand et al. teach that delivery is a very similar issue for both approaches and that siRNAs are very promising tools for gene inhibition *in vivo* (see page 1000, column 2).

Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity (see page 4503). Braasch et al. teach goals for improving oligonucleotides including: improve pharmacokinetics, tissue distribution, and targeting; characterize the mechanism of RNA interference and its full potential for inhibition of gene expression for cell culture studies; use RNAi for in vivo inhibition of mammalian gene expression; perform comparative studies to demonstrate the relative strengths of different oligomer chemistries for given applications (i.e. morpholino versus RNAi) (see Table 2). Braasch et al. teach that if good *in vivo* uptake can be achieved, RNAi might significantly improve the ability of oligonucleotides to have an impact (see page 4509).

Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. added chemical modifications to ribonucleotides at either of the two ends of an oligonucleotide sequence, or the center region together with different combinations of phosphodiester/phosphorothioate backbones and investigated the effect on the activity of antisense oligonucleotides. The

gapmer oligonucleotide exhibited a potent bispecific antisense activity. Olie et al. teach that gapmer chemistry is an optimal format and that these findings may have implications for the design and development of antisense oligonucleotides. Olie et al. teach that 2'-O-modifications provide additional nuclease resistance to oligonucleotides. Olie et al. teach synthesis of 20-mer chimeric antisense oligonucleotides.

It would have been obvious to synthesize a siRNA with the structural characteristics taught by Elbashir et al. with modifications within the instant genus and wherein 10 or more pyrimidines are modified with the instant modifications.

Furthermore, it would have been obvious to incorporate each of the instant types of chemical modifications or combinations of chemical modifications, as each of the types of modifications are taught by Elbashir et al., Matulic-Adamic et al., or Parrish et al. to enhance nucleic acid inhibitory molecules.

It would have been obvious to incorporate the modifications differentially between purines or pyrimidines because the genus of possible places to incorporate the known modifications is very small (pyrimidine or purine). When incorporating modifications in nucleic acids, the modifications are incorporated into a purine or a pyrimidine. Given that the modifications were known in the art to benefit nucleic acid stability, and it was known to incorporate the same modifications from antisense/ribozyme technology into siRNAs, wherein the only possible places to incorporate the modifications is on a purine or a pyrimidine, it would have been obvious to incorporate the instant modifications into at least 10 nucleotides of the sense and/or antisense strand in combination with the specific modification of 10 or more pyrimidines and this is considered within the realm of

routine optimization.

One would have been motivated to synthesize a siRNA molecule, as taught by Elbashir et al., and to incorporate the modifications of Nyce given that Nyce teaches antisense oligonucleotides and teaches modifications thereof (phosphorothioate, 2'-deoxy and 2'-O-methyl modification of the oligonucleotides at various percentages of the purine and/or pyrimidine residues, including 100% substitution (see page 73)) for enhancing the uptake of the oligonucleotides. Therefore, one would have been motivated to incorporate the same types of modifications into a siRNA for the same purpose of enhancing uptake of the molecule, especially given that Bertrand et al. teach a comparison of antisense oligonucleotides and siRNAs and teach that siRNAs appear to be quantitatively more efficient with a longer lasting effect *in vitro* than antisense oligonucleotides. Furthermore, Bertrand et al. teach that siRNA technology can be applied in the same delivery situations that have been previously studied with antisense oligonucleotides.

One would have been motivated to incorporate 2'-deoxy-2'-fluoro modifications, as taught by Parrish et al. or Matulic-Adamic et al., as well as 2'-O methyl, 2'-deoxy modifications, and phosphorothioates, as taught by Matulic-Adamic et al., as each of these chemical modifications, as well as various combinations of chemical modifications, were known in the art to protect nucleic acids from exonuclease degradation and enhance the activity of nucleic acids, as taught by Matulic-Adamic et al. One would have been motivated to incorporate the modifications on purines or pyrimidines as a matter of optimization of the activity of the siRNA, given there are only

two choices.

The instant genus is very broad. It is considered that there would be some configuration of the chemical modifications that were known in the art to benefit other nucleic acid molecules such as antisense oligonucleotides or ribozymes that would retain RNAi activity when incorporated into nucleic acid molecules. Due to the breadth of the instant claims, the teachings of Elbashir et al. are considered to be motivation with regards to extensively modifying nucleic acid duplexes to optimize the activity therein. Although Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity, there are no instant claims that are identical in scope to the teachings of Elbashir et al. Therefore, within the huge genus of molecules that are being instantly claimed, the teachings of Elbashir et al. are considered to offer motivation to test various types of known chemical modifications at different percentages in order to optimize the activity of the molecule.

It is noted that ribozymes are sequence specific inhibitory nucleic acid molecules that rely on activity with a complex secondary structure. Although ribozymes are faced with the complexity of structure, it is well known in the nucleic acid art to incorporate extensive levels of chemical modification to enhance the activity of the molecule and to specifically incorporate each of the instantly recited modifications, as evidenced by Matulic-Adamic et al.

The instant specification discloses a multitude of oligonucleotide and ribozyme art regarding chemical modifications and teaches that "Such publications describe general methods and strategies to determine the location of incorporation of sugar,

base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of these teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to promote RNAi in cells is not significantly inhibited." (see pages 109-110).

It is acknowledged that the specification is not to be relied upon for a source of motivation and that is not considered to be the instant case. The specification is merely being relied upon to distinguish that applicant recognized that double stranded nucleic acid modification is dependent upon the state of the art of oligonucleotides and ribozymes and that previously beneficial chemical modifications would be used with double stranded nucleic acid molecules as well.

Furthermore, Braasch et al. teach that the need for antisense oligomers that are more potent and more selective has been widely recognized and has led to the development of chemical modifications to improve binding and selectivity. Braasch et al. further recognize that goals to improve RNAi can be accomplished by utilizing chemical modifications. Since Braasch et al. teach that chemical modifications yield more potent and more selective antisense oligomers, such as oligomers for RNAi, and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, the gene expression of Elbashir et al. and Parrish et al. being inhibited by RNAi, one would have been motivated to synthesize duplexes with different levels of modifications to optimize the activity of the molecule.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters the same problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

For example, Olie et al. teach that gapmer oligonucleotide chemistry, wherein three distinct regions are present, has provided antisense oligonucleotides with increased efficacy and reduced non-antisense-related toxicity. Olie et al. teach that combinations of different modifications at different regions of the oligonucleotide have been tested in order to optimize oligonucleotide activity. Olie et al. teach stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Olie et al. is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations and amounts, as taught by Olie et al., into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes or siRNA duplexes, as evidenced by Elbashir et al., Nyce, Matulic-Adamic et al., Parrish et al. and Olie et al., wherein each of the molecules face similar delivery challenges, and each of which can be improved with

modifications, as evidenced by Braasch et al. Since Olie et al. teach effectively walking modifications across antisense oligonucleotides to optimize the combination of modifications as well as the location of the modifications and Elbashir et al. and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for modifications at various percentages to benefit the double stranded nucleic acid molecules of Elbashir et al.

Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach extensive modification of double stranded nucleic acid molecules and Olie et al. teach experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating the modifications at various percentages in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would

have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/170,290. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '290 are specific for a BACE gene, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/185,652. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short

interfering nucleic acid molecules of the claims of application '652 are specific for a human c-Fos RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/204,572. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '572 are specific for a human ECGF1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/203,055. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short

interfering nucleic acid molecules of the claims of application '055 are specific for a human VCAM-1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/200,736. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '736 are specific for a Cyclin D1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/203,731. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short

interfering nucleic acid molecules of the claims of application '731 are specific for a human CHRM3 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/204,612. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short interfering nucleic acid molecules of the claims of application '612 are specific for a human MMP13 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/175,367. Although the conflicting claims are not identical, they are not patentably distinct from each other because each of the claim sets are directed to double stranded nucleic acid molecules with overlapping structural characteristics (sizes, modifications, compositions, etc.). The double stranded short

interfering nucleic acid molecules of the claims of application '367 are specific for a human HIF1 RNA sequence, which anticipates the instant genus of any target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 52 and 54-64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 129-138 of copending Application No. 10/444,853. Although the conflicting claims are not identical, they are not patentably distinct from each other because the conflicting claims are directed to double stranded nucleic acid molecules with substantially similar and overlapping structural characteristics, wherein the instant claims do not recite a target.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant requests that the double patenting rejection be held in abeyance.

(10) Response to Argument

Response to Arguments--Claim Rejections - 35 USC § 103

Applicant argues that attempts at more extensive modification beyond the 3' termini was taught to reduce the ability of siRNAs to mediate RNAi in view of the

teachings of Elbashir et al. Applicant has continued to mischaracterize the teachings of Elbashir et al.

Applicant argues that Elbashir et al. teaches away from modifying more extensively than what is shown in Figure 4 because 50% and 100% modification abolished activity. Applicant continues to draw conclusions of the teachings of Elbashir et al. that are outside of the data and teachings of Elbashir et al. Elbashir et al. teaches 19% successful modification and teaches that 50% or 100% (one or both full strands) with 2'-deoxy or 2'-O-methyl (one modification only) abolished activity. Elbashir et al. does not teach any other data. Therefore, the only thing that Elbashir et al. teaches away from is 100% modification of one or both strands with 2'-deoxy only or 2'-O-methyl only. None of the instant claims are identical to this teaching and therefore Elbashir et al. does not teach away from the instant claims. Although applicant continues to read the passage on page 6885 of Elbashir et al. out of context, the only "more extensive" modification that could be referred to is the complete modification of one or both strands, as from a full reading of the article is the only modification that was tested outside of the 2 or 4 nucleotides on each end.

It is noted that the interpretation of the Elbashir et al. (Tuschl) reference is argued in detail by applicant. However, the interpretation of the article has already been decided by the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858), and the interpretation is consistent with that of the examiner in the instant rejection.

On page 27 of the decision, the board sets forth that appellant's argument that Tuschl teaches avoiding any 2'-O-methyl modifications is unpersuasive and misstates the teachings of Tuschl. A fair reading is that more extensive 2'-deoxy or 2'-O-methyl modification beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi. Stating that complete substitution abolished RNAi is not the same of stating that any 2'-O-methyl modification should be avoided. It is noted that when incorporating chemical modifications into nucleic acid inhibitory molecules, it is routine to balance stability and activity. Therefore, it is a matter of routine optimization to determine an acceptable balance between a reduction in activity and an increase in stability, as long as the molecule is still in fact active.

The decision also sets forth that nucleic acid molecules are known to be degraded or hydrolyzed by nucleases *in vivo* and in culture systems and thus it is routine in the art to modify nucleic acids to resist nuclease hydrolysis, and particularly to modify with modifications that were known to enhance stability. Similarly, capping as disclosed by Matulic-Adamic et al. would be reasonably expected to sterically interfere with the active site of a nuclease (see page 25 of decision, for example).

It is well recognized in the nucleic acid inhibitor art that some types and levels of modification will yield active molecules, and some will not, thus resulting in a need for routine optimization. Applicant appears to have set forth some type of guideline requiring for every embodiment tested by Elbashir et al. to have resulted in activity. However, Elbashir et al. does teach successful modification, which would motivate one of skill in the art to incorporate modifications and test different levels of modification.

The same types of chemical modifications that have been used routinely in the antisense and ribozyme art have been used in the RNAi art as well and have produced active molecules when routinely optimized.

The instant claims are not directed to any specific pattern of modification that yielded an unexpected property, but rather are directed to a very broad scope of possible modifications at varying positions depending on the target sequence, given that the claims are not directed to any specific target.

Elbashir et al. in no way teaches away from the instant claims, which are not commensurate in scope with the 100% modified duplexes that were inactive of Elbashir et al. Elbashir et al. offers motivation to incorporate modifications to reduce the cost of RNA synthesis and to enhance RNase resistance of siRNA duplexes (see page 6885, column 1). The fact that Elbashir et al. is silent as to modification between 19% and 100% (of one or both strands) would in fact motivate the skilled artisan to modify more extensively than the 19% to optimize the activity/stability balance.

Applicant sets forth that Elbashir et al. teaches siRNA molecules having from 9.5% to 100% modification. However, this statement is not accurate given that Elbashir et al. does not teach data covering this entire range or representative of this range in any manner. The examiner is relying strictly upon what is actually taught by Elbashir et al.

Applicant argues that the review by BPAI of Elbashir that more extensive modification beyond the 8/42 positions reduced the ability to mediate RNAi is consistent with applicant's interpretation that Elbashir et al. teaches away from further modification.

This conclusion is in error given that reduction in the ability to mediate RNAi still yields molecules that are active. It is widely accepted in the nucleic acid inhibitor field that a balance is needed between stability and activity and thus a reduction in activity is often accepted to gain stability, as long as the molecule is still active. The claims do not require any specific level of activity. Applicant erroneously interprets the decision by the board as consistent with a teaching away by Elbashir et al.

The minimum required by the instant claims in fact is not far off from what was exemplified to work by Elbashir et al., given that the instant modifications can be concentrated in the terminal regions.

With regards to Parrish, applicant argues combinations of modifications, although this is not an element that is even required by the instant claims, as all of the modifications can be of the same type. Applicant argues that Elbashir should have taken a different approach based upon the results of Parrish if consistent with the examiner's interpretation. However, the fact that Elbashir focused on a different approach than hypothesized by applicant is irrelevant.

Applicant argues that Parrish et al. teach away from the instant claims. The basis of such an assertion is unclear given that Parrish teaches extensive 2'-deoxy-2'-flouro uridine modification with strong RNAi activity. The 2'-deoxy-2'-flouro uridine modification represents a dsRNA that was extensively modified and acted via RNAi. Although applicant continues to argue elements that are not claimed, applicant has not argued the fact that Parrish teaches a dsRNA with 2'-deoxy-2'-flouro uridine modification that resulted in strong activity. There is no reason to expect that shorter

dsRNAs, wherein Parrish itself teaches that duplexes 26bp in length act via RNAi, would not remain active with the same modification, particularly given that the long dsRNA of Parrish was necessarily cleaved via Dicer in the cell into short siRNA molecules in order to be loaded into RISC and be active. Applicant's assertion regarding Parrish teaching away from 2'-deoxy modifications is completely unfounded given that Parrish specifically teaches 2'-deoxy incorporation with strong RNA interference activity. Applicant points to other examples in Parrish where modification of cytidine to deoxycytidine produced a substantial decrease in interference. Importantly, this does not negate that Parrish teaches a dsRNA with 2'-deoxy-2'-flouro uridine modification that resulted in strong activity. Furthermore, it is well known in the RNAi art that there is a need to balance activity and stability. Modifications that decrease activity are often incorporated to enhance stability as long as the molecule is in fact still active. The teaching pointed to by applicant in no way teaches away from pyrimidine modification and is certainly not commensurate in scope with the instant claim breadth.

There would have certainly been a reasonable expectation of activity within the instantly claimed genus of molecules given the motivation to routinely optimize siRNA molecules via balancing stability and activity wherein the molecules are readily tested and screened via routine techniques in the art. One would reasonably expect that routine optimization via adding modifications to test for stability and preservation of half life would result in active molecules when utilizing modifications that are routinely utilized to enhance the activity of nucleic acid inhibitory molecules.

Applicant points to *KSR International Co. v. Teleflex Inc.* (127 S. Ct. 1727 (2007)) to argue that the instant claims are directed to a new combination wherein the result cannot be predicted. As explained above, the instant claims are directed to a huge genus of modifications and combinations thereof, wherein the schematic is entirely target sequence specific. One would have been motivated to combine the prior-art elements and expect active molecules within the instant claim breadth. It is well within the grasp of the skilled artisan to select and combine known elements within the instant huge genus and to expect active molecules upon routine optimization of the placement of such modifications given the teachings in the nucleic acid inhibitor art. It is the routine optimization of the placement of the modifications that is relied upon for determining activity of such molecules, as it was known to perform such routine testing, as evidenced by the instant references.

In view of *KSR International Co. v. Teleflex Inc.*, when a combination of admittedly old elements produces a new and beneficial result never attained before, it is evidence of invention. However, in the instant case applicant is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in view of the teachings of the prior art.

Applicant argues that some direction in the prior art that would provide a reasonable expectation of success is required. It is believed that the examiner has explained the teaching of the prior art and how these teachings would result in a

reasonable expectation of success within the instant genus. The instant types of modifications were routinely used in the nucleic acid inhibitor art.

Applicant points to specific species within the instant genus in the instant specification and compares the molecules to those of Elbashir et al. Again, the instant genus is huge depending on the target sequence and combination/quantity of each type of the instants modifications. Applicant is pointing to species that are not representative of the instant genus and do not represent unexpected results for the instant genus.

Armed with not only the teachings of Elbashir et al., but the combined teachings of each of the instantly cited references, the skilled artisan would have been motivated to incorporate the modification in different combinations and locations within the duplex within the instant genus and would expect to result in active molecules. The unmet need, as required by KSR, is that of balancing stability and activity with known chemical modifications.

Although applicant asserts that the instant claims require specific combinations of modifications at specific positions, the instant claims recite multiple types of modifications that can be incorporated alone or in various combinations with other modifications, rather than any one specific combination of modifications that have shown some unexpected property. Furthermore, the only positions that are specified are purines vs pyrimidines, of which there are only two choices for the skilled artisan to incorporate modifications at. The claims are not directed to any specific target sequence and therefore the incorporation at purines or pyrimidines varies depending on

the specific target sequence. Therefore, each of these elements is variable rather than directed to a specific configuration as asserted by applicant.

The references collectively set forth that each of the instant types of chemical modifications were routinely incorporated into various types of inhibitory nucleic acid molecules (ribozymes, antisense, dsRNA, or siRNA molecules); that it was known to utilize the same types of chemical modifications from one nucleic acid chemistry to the other, as each faces similar delivery challenges; it was known to optimize such molecules via testing different combinations or locations of incorporation; and it was known to target genes in a sequence specific fashion. The modifications of Parrish et al. are specific to pyrimidines. Furthermore, as explained in the rejection under 35 USC 103(a) above, there are a finite number of choices for positions of incorporation (purine or pyrimidine).

The majority of applicant's arguments appear to be upon the assumption that the instant claims are closed to a specific pattern. However, this is not the case. Although applicant asserts that a specific pattern is being claimed, the instant genus is very large, wherein applicant has not demonstrated any unexpected property of such a large genus given the motivation in the prior art to incorporate the same types of modifications, wherein the modifications would necessarily need to be incorporated into purines or pyrimidines. Each of the elements of the instant claims (modification types, purine vs. pyrimidine, and caps) are routinely optimized in the siRNA art. The specific types of modifications are commonly utilized, the only choice of position is purine vs. pyrimidine

wherein the claims are not directed to any specific target, and terminal caps are routinely utilized to protect the ends of the molecule.

Applicant argues that there would not have been a reasonable expectation of success. Contrary to applicant's argument, this is not true given the instantly claimed genus. It was well within the technical grasp of the skilled artisan to combine chemical modifications that were known and routinely used to enhance stability of nucleic acid therapeutic molecules to arrive at molecules within he instantly claimed genus that would likely have activity, as it was known in the art to balance stability and activity via routinely testing different combinations/quantities of such modifications.

Applicant continues to argue the teachings of this reference via drawing their own conclusions as to results between the 19% successful modification and 100% unsuccessful modification of Elbashir et al., experiments that simply are not addressed via Elbashir. Applicant points to page 6885 of Elbashir et al. and interprets the passage as teaching away from producing extensively modified duplexes. This passage is interpreted by both the examiner and the board as referring to the only extensive modification that is taught by Elbashir et al., which is 100% modification. Elbashir et al. is completely silent as to modification between 8/42 positions that was successful and 100% modification of one or both strands with a single type of modification that was unsuccessful.

It is noted again that there are only two options to incorporate the instant modifications, purine or pyrimidine; wherein the quantity and location of purines or

pyrimidines is entirely target sequence specific, although the instant claims are not closed to any specific target.

Applicant argues the Elbashir et al. reference again and sets forth that Elbashir attempted to stabilize molecules but failed in providing molecules that are stable and active. The basis of this argument is unfounded given that Elbashir et al. does teach active molecules that are modified. It is believed that the examiner has explained exhaustively that Elbashir et al. does not teach away from the instant claim scope in any manner, which is supported by the interpretation by the board.

Applicant argues that the instantly claimed compounds have demonstrated unexpected results. However, the data relied upon is not commensurate in scope with the instantly claimed genus, given that the instant claims embrace a huge genus resulting from many possible combinations of types of modifications at a very large genus of possible positions depending on the specific target sequence. The comparison set forth by applicant is comparing one specific duplex of Elbashir, which is not demonstrative of any target sequence or even selection of the position of the modifications within the duplex of Elbashir et al. Elbashir et al. concentrated on the terminal regions of the siRNA duplex and simply offers motivation to test for incorporation of modifications at other positions. Simply setting forth a duplex that yielded better results does not mean that the instant genus has an unexpected property.

Response to Arguments—Double Patenting

Applicant argues that each of the applications have claims directed to a selection invention, i.e., an invention that is patentably distinct over the instant claims. Applicant argues that the claims of the conflicting applications are either directed to a specific target or two a two-tiered modification configuration wherein the pyrimidines and purines each have specific types of modifications.

With regards to the claim sets that are directed to specific targets, these species anticipate the instantly claimed broad genus that is not directed to any specific target. Furthermore, the instant claims specify pyrimidine modifications and therefore the claims of the conflicting applications and the instant claims are directed to overlapping subject matter. The instant claims embrace the modifications required by the conflicting applications.

(11) Related Proceeding(s) Appendix

Copies of the court or Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/AMY BOWMAN/

Primary Examiner, Art Unit 1635

Conferees:

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1636

/Jon D. Epperson/
Primary Examiner